II. REMARKS

Claims 1 to 17 are pending in the subject application. By this Amendment and Response, claims 1, 2, 8, 11 and 15-17 have been amended. New claims 18 and 19 have been added. Support for the amendments to the claims and the new claims is found in the specification on page 5, lines 20 to 30; page 6, lines 17 to 29; and page 7, line 18 to page 8, line 25. Accordingly, an issue of new matter is not raised by these amendments and entry thereof is respectfully requested.

In view of the preceding amendments and the following remarks, reconsideration and withdrawal of the outstanding rejections is respectfully requested.

Objection to the Specification

The Office acknowledged Applicant's amendments and response to the Office Action of August 9, 2002, submitted December 16 and 18, 2002. In view of these remarks, the Office removed the objection and rejections under 35 U.S.C. § 112 of the previous Office Action.

35 U.S.C. § 102

Claims 1-5 and 9, 11-12 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Periostat (doxycycline capsules). The Office alleged that Periostat (doxycycline capsules) teaches twice a day administration of doxycycline to adult patients (see Clinical Study page 945 in particular).

Claims 1-5 and 10 also stand rejected under 35 U.S.C. 102(b) as allegedly anticipated by McKearn et al. (WO 00/38717). The Office argued that McKearn et al. (WO 00/38717) teaches a method comprising employing matrix metalloproteinase inhibitor in combination with radiation therapy (citing the abstract). The Office also alleged that McKearn et al. (WO 00/38717) further teaches the following MMPs, specifically: Marimastat, Metastat, Bay-12-9566 and D-2163 (citing page 71).

Applicant respectfully traverses. Claims 1 and 2 have been amended herein to more clearly define the invention of the claims, i.e., that a population of patients that are susceptible to

liver disease due to chemotherapy or radiation therapy can be treated by administration of an effective amount of an MMP inhibitor. Administration of an effective amount of an MMP inhibitor also is a prophylactic therapy for liver disease when patients undergo chemotherapy or radiation therapy.

The cited prior art does not teach or suggest, nor enable, one of skill in the art to practice the invention of the claims. The Periostat reference teaches a twice a day administration of doxycycline to adult patients in an amount that is less than 50 times the amount required by the claims. It does not teach or suggest administration of doxycycline to patients susceptible to liver disease as a side effect of radiation therapy or chemotherapy. McKearn et al. teaches a combination of radiation and administration of an MMP inhibitor to treat neoplasia. Similar to the Periostat reference, it also does not teach or suggest the administration of an MMP inhibitor to treat or prevent liver disease which is a side effect of radiation therapy or chemotherapy. Similar to the Periostat reference, the amount effective to achieve the object of the subject invention is logs different from the "effective amount" required by the claims.[1]

Thus, the cited references do not anticipate the claims of the subject application. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102 is respectfully requested.

35 U.S.C. § 103

Claims 1-6, 9,11-13 and 16 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Periostat (doxycycline capsules). The Office alleged that Periostat (doxycycline capsules) teaches the administration of 20 mg twice a day of doxycycline to adult patients (citing the Clinical Study appearing on page 945). However, the Office acknowledged that Periostat (doxycycline capsules) does not teach the administration of 15 mg twice daily of doxycycline to an adult patient. However, the Office stated that it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer 15 mg twice daily of doxycycline to adult patient and that one of ordinary skill in the art would have been motivated to administer 15 mg twice daily of doxycycline to a patient because optimization of amounts is within the skill of the artisan and is therefore obvious.

[1] Note, Applicant has amended claims 8, 15 and 17 to correct a typographical error that appeared in the claims as filed. Support for this correction is found on page 8 of the original application papers.

Claims 4, 7-10, 14-15 and 17 stand rejected under 35 USC § 103 as allegedly unpatentable over McKearn et al. (WO 00/38717) and Watanabe et al. (USPN 6,150,394). The Office cited McKearn et al. (WO 00/38717) for allegedly teaching a method comprising employing matrix metalloproteinase inhibitor in combination with radiation therapy. McKearn et al. (WO 00/38717) also is alleged to teach the following MMPs specifically: Marimastat, Metastat, Bay-12-9566 and D-2163 (citing page 71).

Watanabe et al. (USPN 6,150,394) is cited for allegedly teaching a method comprising administering 0.01 mg/kg/day to 100 mg/kg/day of compositions comprising MMPs of formula I (which encompass 2-[(4-biphenylsulfonyl)amino]-3-phenyl-propionic acid, citing col. 19, lines 13-35 of the patent). Watanabe also allegedly teaches that its compositions can be administered parenterally (citing col. 19, lines 3 7-47 of the patent).

The Office argued that although McKearn et al. (WO 00/38717) and Watanabe et al. (USPN 6,150,394) taken together do not specifically teach the 100-200 mg/hour administration of 2-[(4-biphenylsulfonyl)amino]-3-phenyl-propionic acid in their methods of administering MMPs, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer 100-200 mg/hour of 2-[(4-biphenylsulfonyl)amino] -3-phenyl-propionic acid to the patient. The Office argued that the motivation to administer 100-200 mg/hour of 2-[(4-biphenylsulfonyl)amino]-3-phenyl-propionic acid to a patient arises from optimization of amounts and such is within the skill of the artisan.

The Office also remarked that Applicant's arguments filed December 16, 2002 have been fully considered but are deemed to be not persuasive. The Office stated that Applicant's prior arguments regarding the disclosure of Periostat as not enabling, is not persuasive since claims 1-5, 9 and 11-12 do not designate a particular host. The Office stated that the method herein simply requires the administration of a metalloproteinase inhibitor and that the host need not have a particular condition, disease or disorder. The Office remarked that all hosts need a prophylactic measure against liver disease in general and Sinusoidal Obstruction Syndrome specifically so long as an MMP has been administered in the regimen claimed herein the claimed limitations are met and that so long as the same amount of the same substance is administered to a host, the method claimed herein is anticipated.

However, the Office acknowledged that Applicant's arguments with respect to the

rejection(s) of claim(s) 10 under 35 U.S.C. § 102 were persuasive and that the rejection now includes claims 1-5 in addition to claim 10.

Applicant respectfully traverses the grounds for rejection under 35 U.S.C. §·103. Applicant has now amended the claims to specifically recite that the population receiving the MMP inhibitor is in need of such therapy. None of the cited references, alone or in combination, teach or suggest the invention of the amended claims, i.e., administration of an MMP inhibitor to a specified patient population. Additionally, the "effective amount" required by the claimed invention is so far removed from the recommended dosages of the cited art that it would require an undue amount of experimentation to arrive at the claimed invention based on the disclosures of the cited references. In other words, to achieve the invention of the claims more than ordinary skill and routine experimentation were required. The invention is more than mere optimization of dosage ranges disclosed in the cited references.

In view of the preceding amendments and remarks, reconsideration and withdrawal of the rejections of the claims under 35 U.S.C. § 103 is respectfully requested.

III. CONCLUSION

If the Examiner determines that a telephonic interview would advance prosecution of the application, the Examiner is invited to telephone Jennifer Phelps at (213) 680-6459.

If the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-2518**, referencing no. 7000692001. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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